Steroid hormones synthesis

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By the end of this lecture the student will be able to:

- Discuss different types of steroid hormones regarding sites of synthesis , secretion, transport and biological effects
- Illustrate steps of different pathways of biosynthesis of steroid hormones
- Determine the mechanism of action of steroid hormones
- Outline the synthesis of steroid hormones in testes and ovary
- Discuss Congenital adrenal hyperplasias and poly cystic ovary

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Steroid hormones:

- **Are group of hormones that belong to the class of chemical compounds known as steroids**
- **All steroid hormones are derived from cholesterol**
- **Sites of secretion : They are secreted by the adrenal cortex, testes, and ovaries and during pregnancy by the placenta & Some peripheral tissues (as adipose tissue & the brain)**
- **They are transported through the blood to their target organs where they perform different physiological functions**
- **Steroid hormones :includes 1-Corticosteroids** 2- **Sex hormones**
- **Corticosteroids that includes:**
- **1-Glucocorticoids e.g Cortisol**
- **2-Mineralocorticoids e.g Aldosterone**
- **Adrenocorticotropic hormone (ACTH) stimulates Glucocorticoids synthesis & secretion.**
- **Sex hormones as Androgens, estrogens, and progestins Which is is regulated by LH & FSH**

Steroid hormones Synthesis

- **Cholesterol is the precursor of all classes of steroid hormones**
- **There is a common metabolic pathway for the biosynthesis of all steroid hormones.**
- **A series of enzymatic steps in the mitochondria & ER of steroidogenic tissues convert cholesterol into steroid hormones.**
- **The first step is the conversion of cholesterol into pregnenolone.**
- **This reaction is the rate limiting step in steroidogenesis and occurs in the mitochondria.**
- **This reaction activated by ACTH.**

****The cholesterol substrate can be :**

- **1-Newly synthesized,**
- **2- Taken up from lipoproteins,**
- **3-Released by an esterase from cholesteryl esters stored in the cytosol of steroidogenic tissues.**

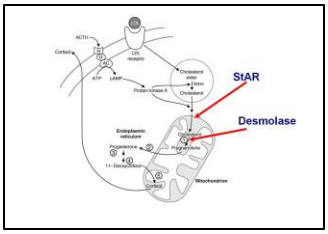
➔ **The cholesterol moves to the outer mitochondrial membrane. An important control point is the subsequent movement from the outer to the inner mitochondrial membrane.**

➔ **This process is mediated by StAR (steroidogenic acute regulatory protein.)**

Steroid hormone synthesis in adrenal cortex:

Glucocorticoids (e.g : cortisol), Mineralocorticoids (e.g : aldosterone), and Adrenal androgens

- **The initial and rate-limiting reaction converts cholesterol(27 carbons) to the (21-carbons) pregnenolone.**



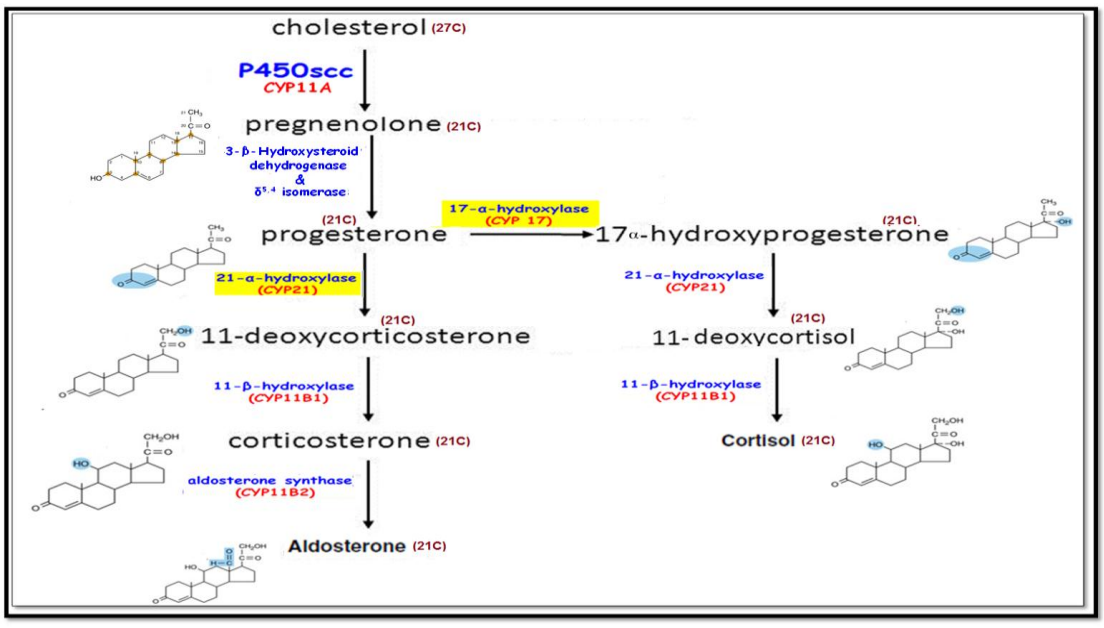
- **Pregnenolone is the parent compound for all steroid hormones.**

  This step occurs also in ovary, and testis

- **Is catalyzed by the cholesterol side-chain cleavage enzyme**

  (A cytochrome P450 mixed function oxidase of the inner mitochondrial membrane)

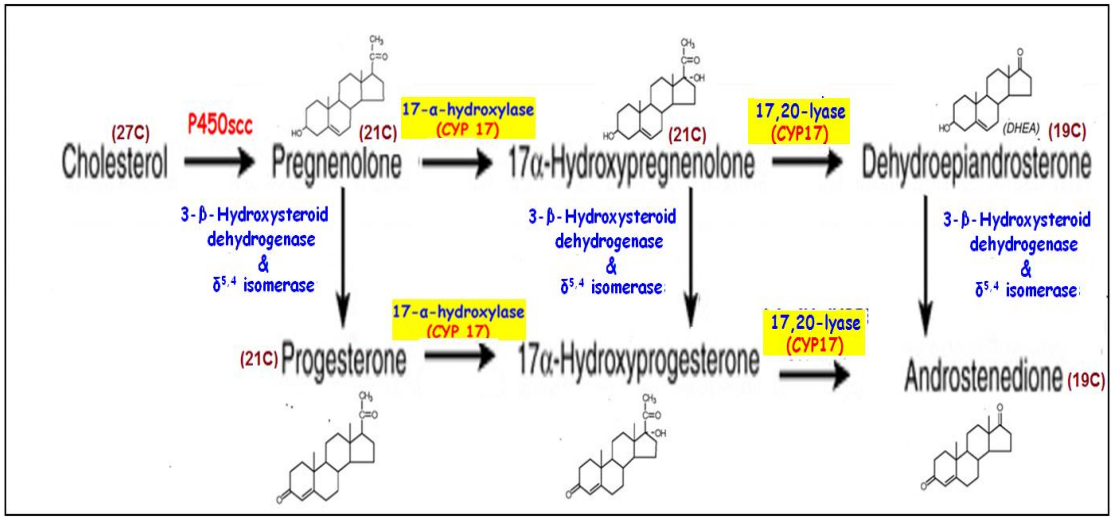
- **NADPH and molecular oxygen are required for the reaction**
- **Note: Pregnenolone is oxidized and then isomerized to progesterone which is further modified to the corticosteriod hormones by hydroxylation reactions that occur in the ER and mitochondria**



Note: 3-β-Hydroxysteroid dehydrogenase and δ5,4 isomerase are the only enzymes in the adrenal pathway of corticosteroid synthesis that are not members of the cytochrome P450 family.

Synthesis of the Adrenal Androgens:

- **Adrenal Androgens are: Dehydroepiandrosterone (DHEA) & Androstenedione)**
- **Both the inner (zona reticularis) & middle layers of adrenal cortex produce androgens**



Note: Although adrenal androgens themselves are weak they are converted in peripheral tissues to testosterone a stronger androgen & to Estrogens.

Note:

CYP17 is bifunctional enzyme has both 17-α-hydroxylase activity & 17, 20-lyase activity.

- **Glucocorticoids and mineralocorticoids contain 21 carbon atoms and have 2 carbon side chain at C-17.**
- **Androgens contain 19 carbon atoms and have keto or hydroxyl group a t C-17.**
- **Because of their hydrophobicity, they must be complexed with a plasma protein:**

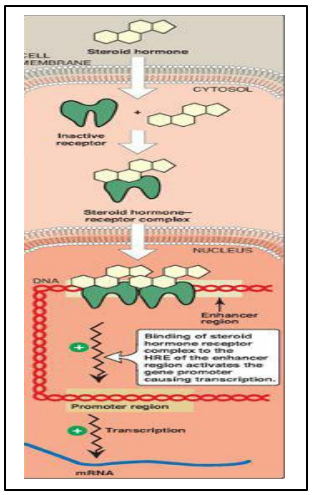
1- Plasma albumin can act as a nonspecific carrier

2- Specific steroid-carrier plasma proteins:

- **Corticosteroid-binding globulin (transcortin) : α_2 globulin is responsible for transporting cortisol**
- **Sex hormone-binding globulin that transport sex hormones: testosterone and estrogens**

1. **Cortisol circulates in plasma In:**
   (8%) free form and (92%) in association of protein.
2. **The free cortisol is the biologically active form of the hormone.**

Mechanism of steroid hormone action {Hormones Group: I}



- **Steroid hormones can across the plasma membrane of its target cell and binds to a specific cytosolic or nuclear receptor.**
- **These receptor–ligand complexes accumulate in the nucleus, dimerize, and bind to specific regulatory DNA sequences [HREs] in association with coactivator proteins.**
- **HRE in association with coactivator or corepressors**
- **of these genes. HREs can also inhibit transcription in association with corepressors.**
- **The HRE interact through a zinc-finger motif with the appropriate sequence on the DNA.**

Synthesis of steroid hormones from gonads:

The testes and ovaries synthesize hormones necessary for sexual differentiation and reproduction

The gonads have 2 functions which are production of germ cells and sex hormones.

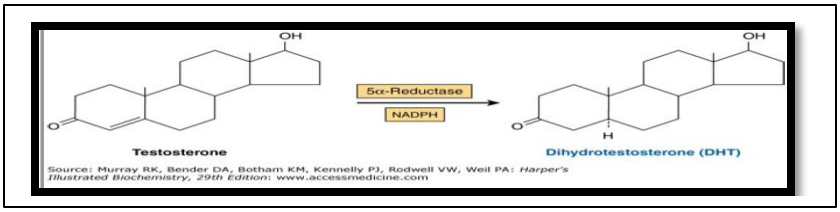
A. In: males: testes produce spermatozoa and testosterone.

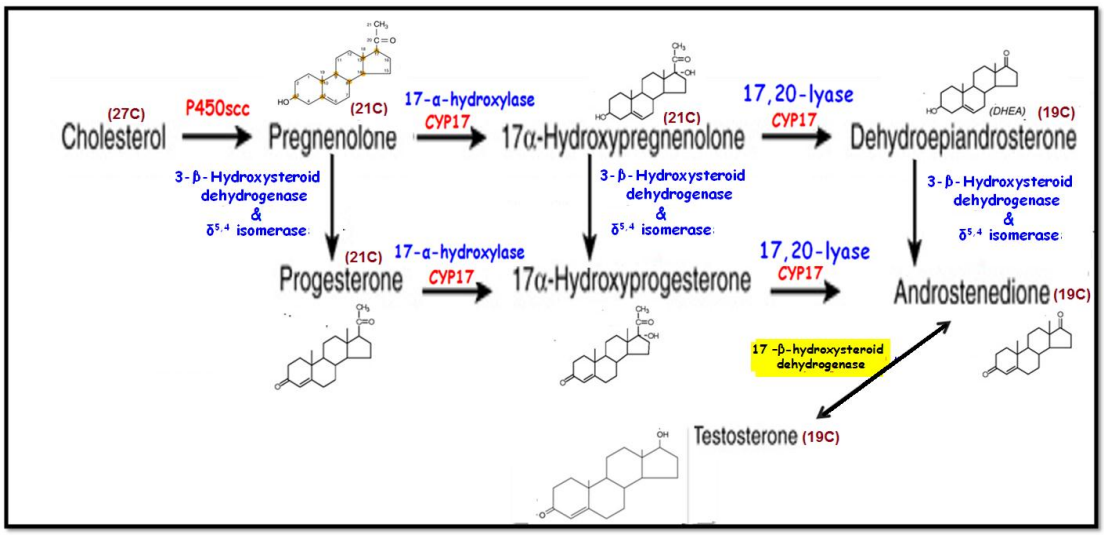
B. In females: Ovaries produce ova and the steroid hormones (estrogens and progesterone).

Testicular steroidogenesis: Is the Synthesis of testosterone by the Leydig cells of the human testicle

Steps:

In its target cells the double bond in ring A of testosterone is reduced through the action of 5 α-reductase enzyme, forming the more potent androgen dihydrotestosterone (DHT)



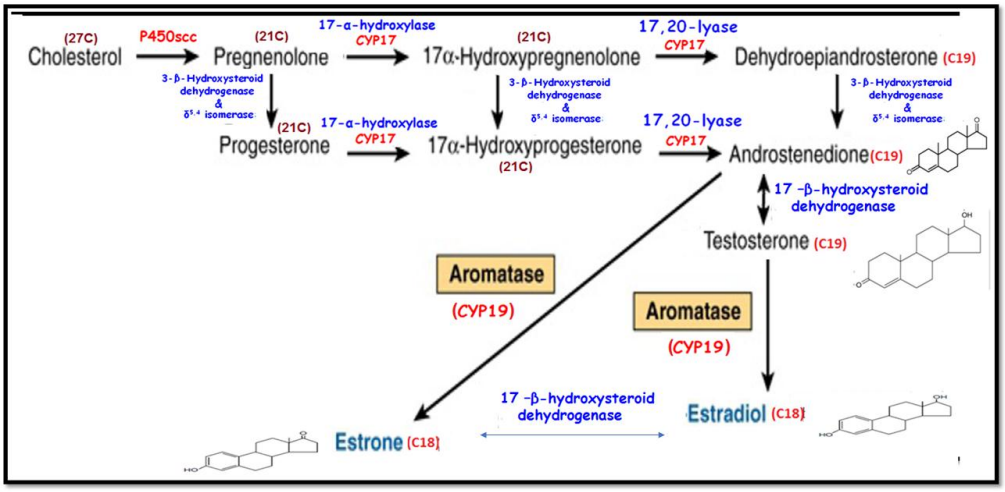


Ovarian steroidogenesis

- **Estrogens are derived from androgens (testosterone & androstenedione) by aromatase enzyme (CYP19).**
- **Theca cells are the source of testosterone & androstenedione.**

  These androgens are converted by the aromatase enzyme in granulosa cells to estradiol (E2) & estrone (E1) respectively.
- **Estradiol, the predominant and most potent of the ovarian estrogens.**

- Steps:



➔ **Note: All Enzymes involved in Steroid hormones are present in the SER except {P450scc, Aldosterone synthase & 11- β –hydroxylase} are mitochondrial enzymes.**

➔ **Steroidogenesis thus involves the repeated shuttling of substrates into and out of the mitochondria.**

- **Aromatase enzyme (CYP19), a member of the cytochrome P450 superfamily.**
- **The aromatase enzyme can be found in many tissues including granulosa cells, adipose cells, liver, skin & other tissues.**
- **Clinical applications:**
- **In obese men, overproduction of estrogen in fat cells can cause gynecomastia = excessive male breast development.**
- **Aromatase inhibitors are used in the treatment of estrogen-responsive breast cancer in postmenopausal women.**
- **Case Scenario: A 5 years old boy was admitted to the clinic, complaining of severe dizziness.**

  On examination, the boy showed signs of premature puberty (hirsutism, enlargement of genitalia, and muscular development).The boy was hypotensive

  Laboratory investigations showed: low serum aldosterone and cortisol levels, hyponatremia, hyperkalemia , and hypoglycemia.

  Enzymatic assay of 21-α-Hydroxylase enzyme, showed deficiency of the enzyme.

  The boy was diagnosed as congenital adrenal hyperplasia, and was treated accordingly

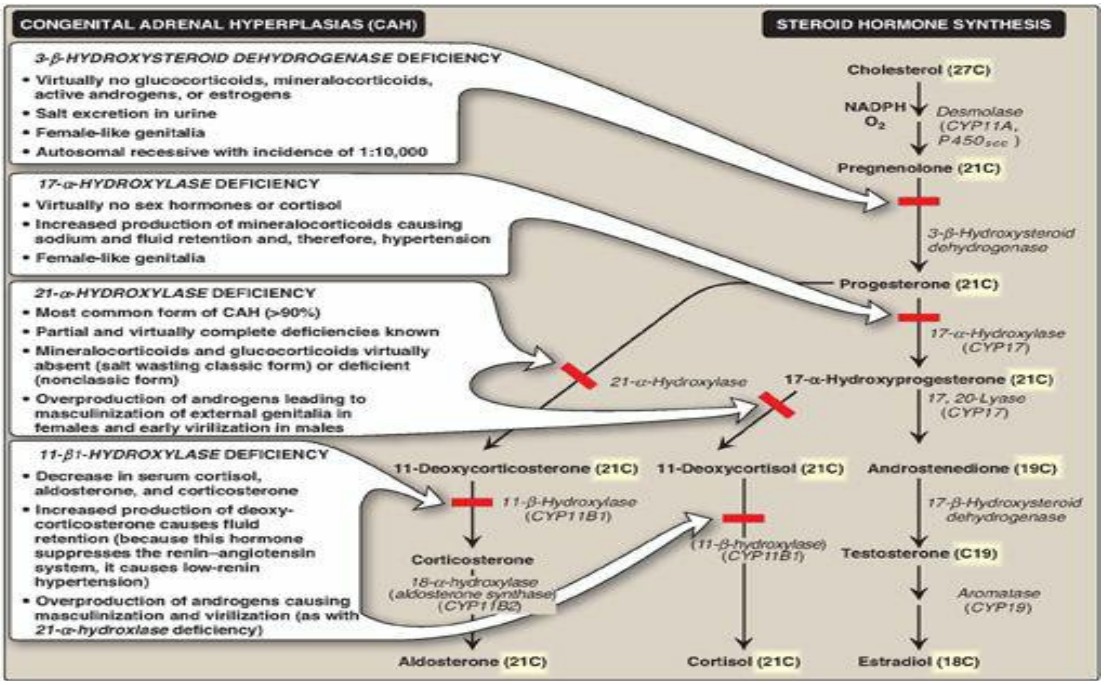
Congenital adrenal hyperplasias (CAH)

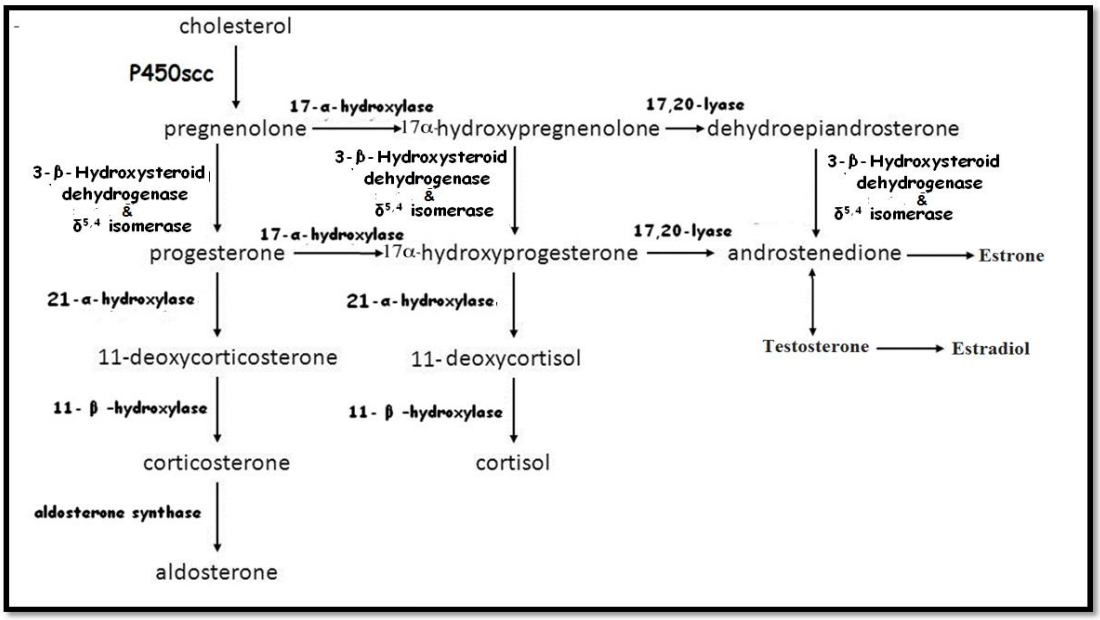
Describes a group of inherited disorders characterized by enzyme defects in the steroidogenic pathways involved in the biosynthesis of steroid hormones

(a group of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the **adrenal** glands)

5 major Enzymes deficiency are clinically important:

- **21-α-Hydroxylase deficiency**
- **11-β-Hydroxylase deficiency**
- **17-α-Hydroxylase deficiency**
- **3-β-Hydroxysteroid dehydrogenese deficiency**
- **20,22 Desmolase deficiency**





21-α-hydroxylase deficiency

- **Most common form of CAH (>90%).**
- **Partially and complete deficiencies are known.**
- **Mineralocorticoids & glucocorticoids are virtually absent (salt wasting classic form) or deficient (non classical form).**
- **Overproduction of adrenal androgens: prenatal masculinization of female genitalia (ambiguous genetalia) & early virilization of males.**

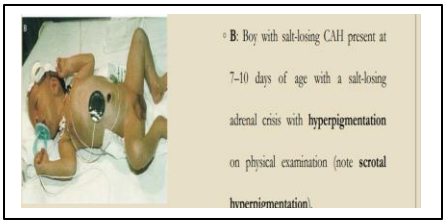
**** Salt wasting classic form:**

- **Clinical pic: Hypotension, Hyponatremia, Hyperkalemia.**

- **Failure to thrive, recurrent vomiting, dehydration, and shock.**

Treatment:

- **Treatment is life-long**
- **Steroid replacement**
- **Plastic surgery for ambiguous genitalia at early age**
- **Genetic counseling**
- **Psychological support**



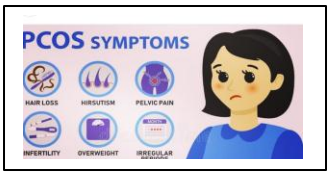
17-α-hydroxylase deficiency

- **Cortisol & sex hormones deficiency**
- **Increased production of mineralocorticoids (aldosterone)**
- **Clinical pic: hypertension, Female like genitalia in males at birth**

polycystic ovary syndrome

Stein-leventhal syndrome

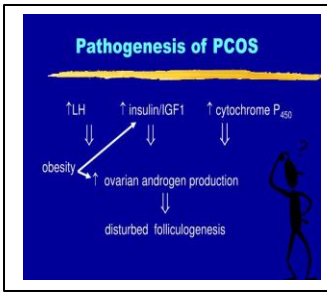
- **most common gynaecological condition affecting women of childbearing age**
- **also associated with the metabolic syndrome**
- **syndrome of ovarian hyperandrogenisation**
- **associated symptoms of Androgen excess**
- **Anovulation leads to menstrual irregularity**



Polycystic ovary syndrome (**PCOS**) is a condition that affects a woman's hormone levels.

Women with PCOS produce higher-than-normal amounts of male hormones.

This hormone imbalance causes them to skip menstrual periods and makes it harder for them to get pregnant.



- **Biochemistry in PCOS**
- **Raised LH or LH:FSH ratio**
- **One or more androgen levels**

(raised testosterone/ androstendione / DHEAS)

- **PCOS is also associated with a characteristic metabolic syndrome that includes:**
- **insulin resistance • dyslipidemia • hypertension**

• These features are linked with increased risks of type 2 diabetes and possibility of premature cardiovascular disease

=====Thank You ======Dr. Marwa Dahpy=====